

Renal collecting ducts: A frontline in protecting against tubulointerstitial injury?

Progressive tubulointerstitial injury is the common pathway to end-stage renal disease (ESRD), but the defence mechanisms against tubulointerstitial injury in acute kidney injury (AKI) and in chronic kidney disease (CKD) are largely unknown. I hypothesise that collecting ducts (CDs) are key defenders of the renal tubulointerstitium and are regulated by retinoic acid (RA) and RA receptors (RARs).

1. *CDs are the only tubular segments that span much of the kidney* and are ideally placed to protect the whole tubulointerstitial compartment.
2. *CDs are resilient* and resistant to dramatic changes in pH, osmotic stress and hypoxia, compatible with a defensive role.
3. *CDs are equipped with specialised pro-repair and pro-regenerative mesenchymal stem cells and defence molecules, e.g. antimicrobial β -defensins and anti-fibrotic microRNAs.* Expression of many genes crucial for renal development, e.g. *Pax2*, *Wnt4* and *Wnt7b*, is also confined to the CDs in adult kidney. It could adapt to pro-repair and pro-regenerative roles.
4. *CDs are uniquely equipped with RA/RAR physiological signalling, which appears indispensable for protecting the kidney and could be therapeutic, if appropriately mobilised.* A defence role for RA/RARs is highlighted by the susceptibility to pyelonephritis and urolithiasis in rats fed a vitamin A-deficient diet; in contrast, vitamin A treatment reduces susceptibility to renal fibrosis in animal models and patients with pyelonephritis. Since RA is effective in treating many models of AKI and CKD, endogenous RA/RARs in CDs may have been evolutionarily selected for protection against injury.
5. *CD defence mediators are tightly regulated and problems arise if dysregulated.* Expression of *Dhrs3*, a negative feedback in RA biosynthesis, depends almost entirely on RA/RAR signalling in CD cells, making any RA/RAR signalling self-limiting. In resolving AKI, CDs are relatively spared and renal RA/RAR activity is increased. In progressive CKD induced by unilateral ureteral obstruction, renal RAR expression decreases, and in mice with diabetic nephropathy there is a kidney-specific impairment of RA/RAR signalling. Work in my laboratory has shown that risk factors for CKD progression, e.g. albuminuria, high glucose, angiotensin II and aldosterone repress RA/RAR signalling in CD cells, while gentamicin, aristolochic acid, vasopressin, endothelin-1 and the neurotransmitter calcitonin gene-related peptide increase signalling. Thus, regulating this pathway in CDs may be a crucial link among renal damage factors in AKI and CKD. To pinpoint a role for RA/RARs at a pan-genomic level, RA/RAR-dependent mRNAs and miRNAs in CD cells have been catalogued, supporting a critical role in defence against infection, inflammation and fibrosis. Thus, RA/RAR signalling in CDs, including its target genes, may serve as a master regulator for defence against tubulointerstitial damage.

Important questions remain: Are CD defences activated in AKI and if so does this occur in all forms of AKI? Is failure of CD defence a cause of more severe AKI, chronicity and CKD progression? What are the roles for CD-specific RA/RAR signalling and gene expression, and CD-derived mesenchymal stem cells in renal tubulointerstitial defence? How do CD cells maintain their resilience? How do CDs protect the tubulointerstitial compartment? Do CDs secrete defence molecules into the urine and express defence biomarkers in biopsied renal tissue? Can these biomarkers predict prognosis and guide treatment? Finally, can novel therapies be devised to amplify CD defences?

In summary, my hypothesis proposes a new role for CDs in renal protection, repair and regeneration, supplementing their role in controlling urinary fluid and electrolyte composition. This hypothesis can be tested by repressing or boosting the expression and activities of key molecules selectively in the CDs and observe the resulting phenotype. Further investigation of this hypothesis could lead to new strategies for prevention, treatment and monitoring of AKI and CKD.